Yttrium-90 hepatic radioembolization: an update on current practice and recent developments

Short Running Title: Current Developments Radioembolization.

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ABSTRACT

Radioembolization is an established treatment modality that has been subjected to many improvements over the last decade. Developments are occurring at a high pace, affecting patient selection and treatment. The aim of this CME review is therefore to provide an overview of current practice, with a focus on recent developments in the field of radioembolization. Several practical issues and recommendations in the application of radioembolization will be discussed, ranging from patient selection to treatment response and future applications.

Keywords: Radioembolization, dosimetry, liver malignancies, hepatic vasculature, yttrium-90
INTRODUCTION

As an established treatment modality for chemoresistant, unresectable hepatic malignancies, radioembolization has expanded its applications in recent years. Radioembolization is based on the administration of $^{90}$Y-loaded microspheres in the arterial vasculature of the liver. Currently two types of microspheres are FDA approved and commercially available: resin microspheres (SIR-spheres®, SIRTex Medical) and glass microspheres (Theraspheres®, BTG International Ltd.). Due to preferential arterial flow, the microspheres occlude small tumor arterioles, thus selectively irradiating tumors. This CME review aims to give an overview of current developments in the field of yttrium-90 hepatic radioembolization.

PATIENT SELECTION

Currently, radioembolization is mainly indicated in a palliative setting of primary and secondary hepatic malignancies, only when other (minimal) invasive or chemotherapeutic treatments have failed. Work-up for radioembolization includes clinical status, hematological/biochemical status, anatomical assessment with CT/MRI, and when appropriate, molecular imaging with SPECT/CT or PET/CT. The (contra)indications (Table 1) need to be assessed by a multidisciplinary team.(1, 2) Unlike many treatment modalities, age is not a contra-indication for radioembolization and has not been shown to alter prognosis.(3, 4)

Sufficient liver function is of primary importance and is regarded the greatest limitation (Child-Pugh-score ≤ B7). Before considering radioembolization (when sufficient liver function is present), portal venous integrity, prior surgical treatments and prior liver-directed treatments need to be evaluated. Compromised portal venous integrity is most commonly caused by a portal vein tumor thrombus (PVT), resulting in a greater dependence of the liver parenchyma on
its arterial supply. (5) Theoretically after embolization, a compromised portal circulation could jeopardize liver function due to ischemia or infarction, induced by the arterial occlusion. However, radioembolization has a low embolic effect and patency of most of the arterial tree is maintained after treatment. (6, 7) Radioembolization in the setting of PVT is therefore safe and can sometimes lead to complete portal vein revascularization, even in main PVT. (8) In contrast to transarterial chemoembolization (TACE), PVT is not considered a contra-indication. Radioembolization is an emerging indication in early-advanced HCC (Barcelona Clinical Liver Cancer (BCLC) C, liver-dominant, ECOG 1-2, PVT). (8) Based on current evidence, application of radioembolization in patients with a Child-Pugh-score > B7 and main PVT should be weighed carefully, due to limited potential survival benefit after radioembolization (4.5 - 5 months in Child-Pugh B patients and 2.5 months in Child-Pugh C patients versus 2.7 – 4.0 months in untreated patients). (9-12)

Prior surgical liver resection is no contra-indication for radioembolization. However, surgical procedures involving the biliary tract may be a risk factor for infectious complications. The incidence of hepatic abscesses after radioembolization in patients with a normal biliary tree, or in the presence of a bilidigestive anastomosis is fortunately low: < 1% (Table 2). (13) This is significantly less compared to < 5% in the general TACE population and 48% - 86% after TACE in the presence of a bilidigestive anastomosis. (14, 15) An aggressive prophylactic antibiotic regimen is therefore not advised. (16, 17) Radioembolization in the presence of a bilidigestive anastomosis seems safe, but needs further attention, as liver abscesses after TACE show a high mortality rate of 11% - 50%. (15, 18) Currently, a bilidigestive anastomosis is considered to be a relative contra-indication for radioembolization, but this is based on available TACE literature due to limited evidence in radioembolization.

HEPATIC VASCULARIZATION AND ANGIOGRAPHIC CONSIDERATIONS
Standard hepatic arterial supply originates from a celiac trifurcation, from which the common hepatic artery (CHA) arises. The CHA becomes the proper hepatic artery (PHA), after the gastroduodenal artery (GDA) has branched off. The PHA continues towards the hilar plate, where it splits into the right and left hepatic arteries. Anatomical variants of the hepatic arterial vasculature are common and correct identification of these variants is essential as it may increase the risk of extrahepatic deposition. Information of the arterial liver vascularization derived from pre-procedural liver CT- or MRI-angiography (e.g. with an early arterial phase) is paramount for successful angiography. Anatomical variants are frequently missed in clinical practice in the absence of a thorough evaluation of the arterial vascularization on multi-modality imaging. This results in unnecessary additional angiography procedures and incomplete radioembolization treatments.

The severity of an extrahepatic deposition of microspheres depends on the affected organ and the number of displaced microspheres, and its location depends on the culprit vessel. Previously, so-called ‘skeletonization’ of the hepatic arteries was advised to avoid extrahepatic depositions. In recent years however, this has been debated. ‘Skeletonization’ can be quite an endeavor and new hepatic-enteric collaterals may develop after coil embolization. Moreover, numerous disadvantages are related to the angiography procedure itself: increased procedure complexity, additional radiation dose, potential vessel damage and complications of coil deployment. At present, most experienced centers try to avoid coil embolization. Significant extrahepatic depositions are mostly found within the distribution of three distinct side-branches (Table 3): the GDA, cystic artery and right gastric artery (RGA). In a recent case series of 134 patients, 68.7% did not undergo coil embolization of either the GDA or RGA. After radioembolization with glass microspheres 1% developed a gastric ulcer. On the other hand, in a case series of 247 patients treated with resin microspheres, 3.2% developed a biopsy
proven gastroduodenal ulcer, despite ‘skeletonization’.(24) Potential culprit vessels need to be assessed and coiled individually. Thus, standard rigorous occlusion of all side-branches of the hepatic arteries (e.g. ‘skeletonization’) has been abandoned.(23)

If an extrahepatic deposition of activity is found on the pre-treatment simulation with \( ^{99m}\text{Tc}\)-macroaggregated albumin \( (^{99m}\text{Tc}\text{-MAA}) \) SPECT/CT, coil embolizing the culprit vessel, a more distal position of the catheter, or superselective catherization can provide a safe treatment procedure, rendering 91% - 96% of the prior selected patients eligible for radioembolization.(25, 26) To avoid the need for a second pre-treatment angiography, using a catheter-directed CT (e.g. C-arm cone beam CT or hybrid angiography/CT) may prove indispensable. The culprit vessels can be identified during angiography and coil embolized immediately (Figure 1).(27) Additionally, C-arm CT can assess tumor coverage during the angiography procedure. Unenhanced tumor regions can be detected, often leading to identification of additional supplying arteries, preventing incomplete treatment. The C-arm CT provides the interventional radiologist with valuable feedback during the angiography procedure and affects the treatment plan in up to 52% of the patients.(28)

**PRE-TREATMENT IMAGING AND DOSIMETRY**

Pre-treatment simulation is currently based on \( ^{99m}\text{Tc}\text{-MAA-SPECT/CT} \) for assessment of extrahepatic depositions and lung shunting. Lung shunting is caused by arteriovenous anastomoses or shunts in the liver parenchyma or tumor, potentially resulting in a radiation pneumonitis after radioembolization.(29, 30) The highest tolerable lung shunt absorbed dose (LSD) was defined as 30 Gy after a single treatment and up to 50 Gy after repeated treatments, in analogy with external beam radiation therapy of the liver.(31) The lung shunt fraction (LSF) is usually calculated by using the counts in a region of interest (ROI) of the lungs, divided by the total counts in a ROI of the lungs plus the liver (including tumor activity). However, this method is
based on planar imaging, and is operator- and institution dependable. Overall, an absolute threshold (in Gy), is preferred over a relative one. Moreover, SPECT/CT leads to more accurate LSD calculation compared to planar imaging. Up to 170% LSD overestimation can occur when calculating LSD on planar imaging compared to SPECT/CT imaging. Elschot et al. determined the lung shunt dose on planar imaging and SPECT/CT by using $^{99m}$Tc-MAA (150 MBq) as well as $^{166}$Holmium-microspheres (250 MBq). The true mean absorbed lung dose based on $^{166}$Ho-SPECT/CT was 0.02 Gy. The lung absorbed dose was significantly overestimated by pre-treatment planar imaging ($^{99m}$Tc-MAA: 5.5 Gy and $^{166}$Holmium: 10.4 Gy), but also by $^{99m}$Tc-MAA-SPECT/CT (2.5 Gy). At present, no alternative for $^{99m}$Tc-MAA is commercially available.

In the absence of significant extrahepatic activity, the only true dosimetric limitation left is the total radiation absorbed dose in healthy liver parenchyma, also called the non-tumor dose ($D_{\text{non-tumor}}$). Little is known about the maximum tolerable $D_{\text{non-tumor}}$ in radioembolization. It varies between patients depending on multiple variables, including distribution of radiation within the non-tumor volume. A $D_{\text{non-tumor}}$ limit < 70 Gy has been proposed ($D_{\text{non-tumor}}$ limit < 50 Gy in cirrhotic livers) although these limits seem quite arbitrarily defined and need to be confirmed in prospective studies. Nevertheless, pre-treatment dosimetry is important to calculate the appropriate prescribed activity. Currently, 4 pre-treatment activity calculation methods are available for commercially available microspheres (Table 4). For resin microspheres, the activity calculation method that was previously used is the ‘empirical method’. This method is solely based on tumor load with a total lack of any other patient-based factors, led to an unacceptable clinical and laboratory toxicity profile, and was therefore abandoned. The second method (‘BSA method’) is semi-empirical and has been used safely in many clinical trials. Its main limitation is the absence of target volume in the calculation method, which can result in an under- (small patient with large liver) or overtreatment (large patient with small liver). Furthermore it does not correct for the individual intrahepatic distribution differences, calculated by the so-called tumor-to-non-tumor ratio (T/N ratio), which is to the
disadvantage of patients with hyper- or hypovascular tumors. Theoretically, embedding the T/N ratio in the activity calculation method for patients with hypervascular tumors will lead to a higher administered dose and higher $D_{\text{Tumor}}$ without compromising healthy liver tissue. The third calculation method, the so-called ‘partition model’, takes most relevant factors into account. The variables are acquired on $^{99m}\text{Tc-MAA-SPECT/CT}$ prior to radioembolization, so no additional procedures are needed.\(^{(37, 38)}\) However, poorly defined tumors pose a problem for segmentation and quantification, and the overall complexity of the partition method renders its use less attractive in daily practice. For radioembolization using glass microspheres, an activity calculation method is advocated without the use of a T/N ratio.\(^{(34)}\) In analogy to the discussion surrounding activity calculation for resin microspheres, the ‘partition model’ based on prior $^{99m}\text{Tc-MAA-SPECT/CT}$ has been shown feasible for glass microspheres as well.\(^{(8)}\)

In daily practice, the BSA-method for resin microspheres and the volume-based calculation method for glass-microspheres are the most commonly applied activity calculation methods for radioembolization. Nonetheless, the ‘partition model’ based on the pre-treatment $^{99m}\text{Tc-MAA-SPECT/CT}$ should be preferred by nuclear physicians and interventional radiologists, because lesion-based dosimetry on the pre-treatment $^{99m}\text{Tc-MAA-SPECT/CT}$ has been shown to correlate with response and survival.\(^{(39-43)}\) The aim of radioembolization is to deliver the highest possible absorbed dose on tumor cells ($D_{\text{Tumor}}$), to induce apoptosis and tumor load reduction. The group of Garin et al. recently showed very interesting results with the use of the so-called partition method for treatment planning of glass microspheres. Treatment planning was based on a target $D_{\text{Tumor}} > 205$ Gy and a $D_{\text{non-tumor}} < 120$ Gy as calculated on $^{99m}\text{Tc-MAA-SPECT/CT}$. In 41 HCC patients with PVT (12/41 main branch) a median overall survival of 18 months was found. Patients with a $D_{\text{Tumor}} > 205$ had a significantly longer progression free survival and overall survival.\(^{(8)}\) The rationale of $D_{\text{Tumor}}$ – response correlations has been supported by clinical studies in different settings.\(^{(39, 44)}\) One should bear in mind however, that
partition modeling based on $^{99m}$Tc-MAA-SPECT/CT, which is influenced by many factors, including discrepancies between $^{99m}$Tc-MAA and $^{90}$Y-microspheres distribution (Figure 2). Several alternatives for $^{99m}$Tc-MAA are currently under investigation, mainly to avoid discrepancies based on morphologic differences between $^{99m}$Tc-MAA and $^{90}$Y-microspheres, and to improve lung shunt quantification.(38)

Since selective treatments are advocated to avoid extrahepatic deposition of activity, the prescribed activity needs to be split according to target volumes. A simple one-third (left lobe) and two-third (right lobe) split is used by some centers, but most centers use the pre-treatment CT for splitting the prescribed activity according to their manual liver segmentation. The most accurate method was proposed by Kao et al., who split the dose according to artery-specific SPECT/CT-based liver segmentation, delineating an artery-specific target volume based on $^{99m}$Tc-MAA distribution.(37) C-arm cone beam CT may also be used for that particular goal.

**TREATMENT**

During administration of resin microspheres stasis of blood flow may occur, leading to incomplete injection of all intended microspheres. This is caused by an embolic effect due to the higher number of resin microspheres (30-50 million), compared to glass microspheres (4 million). The specific activity of resin microspheres (50 kBq/sphere) is approximately 50 times lower than that of glass microspheres (2500 kBq/sphere), but this may vary by shelf-life. While resin microspheres have a stable specific activity during a 24-hour shelf-life, the specific activity (and number of microspheres) may vary for glass microspheres, having a maximum 2-week shelf-life. It has been postulated that a more heterogeneous distribution of glass microspheres leads to a preferable toxicity profile, but vice versa, a more homogeneous distribution of resin microspheres might lead to a preferable efficacy profile.(45) The Northwestern group in Chicago therefore advocated the use of so-called extended shelf-life glass microspheres.(46) These
microsphere characteristics are important to consider when analyzing dose-response relationships. It is not fully understood whether the anti-tumor effect is merely a radiation effect or a combination of an ischemic and radiation effect, especially in the case of resin microspheres. The embolic effect of resin microspheres sometimes leads to acute ischemic pain during injection. Recently however, it was shown that substitution of sterile water for injection by 5% glucose water leads to less pain, less stasis and a more efficient administration. Understanding the flow dynamics during administration will be an important research topic for coming years. It influences tumor targeting and the predictive value of a scout dose for dose distribution and treatment planning.

POST-TREATMENT IMAGING AND DOSIMETRY

Initially, $^{90}$Y-Bremsstrahlung-SPECT/CT was used after radioembolization to exclude extrahepatic activity depositions and to assess intrahepatic microsphere distribution. With 32 positrons per million decays, $^{90}$Y-PET/CT imaging has gradually taken over $^{90}$Y-Bremsstrahlung-SPECT/CT, mainly due to new PET/CT scanners with time-of-flight technology. It allows more accurate quantification and dosimetry.\(^{(47-49)}\) Calculating $D_{\text{Tumor}}$ on post-treatment imaging may predict response.\(^{(50-53)}\) However, evidence was obtained in heterogeneous or small cohorts, mainly in HCC. Furthermore, the available studies differ in applied activity calculation method, used response criteria and type of microspheres administered. Post-treatment imaging allows for the detection of heterogenic distribution of microspheres in the liver and in tumors, which correlates with partial or regional tumor response.\(^{(49-51)}\) In theory, after assessment of these parameters, additional radioembolization may be considered at an early stage, e.g. directly after administration of the treatment dose. However, the safety of repeated whole liver radioembolization has not been firmly established yet.\(^{(54, 55)}\)
Unfortunately, the true definition of the minimal effective $D_{\text{Tumor}}$ (and the maximum tolerated $D_{\text{non-tumor}}$) remains a challenge. The reported $D_{\text{Tumor}}$ thresholds were found to be independent predictors for tumor response and survival, but lesion-based analyses on post-treatment imaging however, show that these numbers range widely.\cite{50, 53} In a follow-up study of 56 HCC patients with 98 tumors, including a quantitative assessment on $^{90}\text{Y}$-PET/CT after radioembolization with glass microspheres, lesion-based analysis yielded a mean $D_{\text{Tumor}}$ of 215 Gy (range 17 Gy - 555 Gy) in responders, defined as partial or complete response according to mRECIST, and a mean $D_{\text{Tumor}}$ of 167 Gy (range 35 Gy - 465 Gy) in non-responders.\cite{53} The true minimal effective $D_{\text{Tumor}}$ remains unknown and needs to be further investigated for each tumor type, tumor size and microspheres used.

Besides tumor dosimetry, $^{90}\text{Y}$-PET/CT allows early assessment of absorbed dose to healthy liver parenchyma: $D_{\text{non-tumor}}$. At present, a $D_{\text{non-tumor}} < 70$ Gy, or $< 50$ Gy in cirrhotic livers, is assumed to be safe by the resin microsphere manufacturer.\cite{33} Nonetheless, $D_{\text{non-tumor}}$ above these limits has been described. Using pre-treatment dosimetry, a $D_{\text{non-tumor}}$ of $< 120$ Gy on treatment planning was accepted for glass microspheres without additional toxicities.\cite{8} Like $D_{\text{Tumor}}$, the maximum tolerated $D_{\text{non-tumor}}$ needs to be refined for baseline liver function, treatment history, tumor characteristics and microspheres used.

**CLINICAL OUTCOME AND TUMOR RESPONSE**

In general, radioembolization is well tolerated. Mild clinical side-effects usually occur within 4-6 weeks after radioembolization (e.g. abdominal pain, nausea, vomiting, fatigue and fever).\cite{2} More serious complications (1-3 months after radioembolization) include complications due to extrahepatic deposition of activity (e.g. gastric ulceration, pancreatitis, radiation pneumonitis) and liver decompensation. Excessive irradiation of healthy liver parenchyma leads to the most serious and life-threatening complication after radioembolization; REILD. This is
thought to be a veno-occlusive disease / sinusoidal obstruction syndrome. Extensive sinusoidal congestion was acknowledged in liver biopsies, affecting the perivenular spaces with hepatic atrophy and necrosis around portal veins with fresh thrombus. In an early stage after radioembolization serum markers show an induction of oxidative stress. Simultaneously, pro-inflammatory pathways are activated, resulting in endothelial injury with the activation of the coagulation cascade. Jaundice and ascites, in the absence of tumor progression or bile duct dilatation, are the main symptoms of REILD. General risk factors for developing REILD include prior chemotherapy, low tumor burden, high baseline bilirubin values and cirrhotic liver disease.

Table 5 features the efficacy results of several landmark studies in the field of radioembolization.

In intermediate and early-advanced stage HCC (respectively BCLC B and C) radioembolization has shown favorable outcomes compared to the currently preferred treatments. Compared to TACE, radioembolization has similar or even better objective response rate (ORR) and similar survival statistics. Moreover, as previously discussed, PVT and bilidigestive anastomoses are no absolute contra-indication. Additionally, an ECOG performance score (PS) ≥ 1 and a large tumor size > 10 cm are currently considered a contra-indication for TACE, in contrast to radioembolization (PS ≤ 2, no tumor size limitation). In large tumors, radioembolization seems to provide effective tumor reduction (Figure 3) and response rates up to 91% have been described.

In BCLC B or C, not suitable for TACE, the current recommendation is systemic treatment with the multikinase inhibitor sorafenib. However, these patients might benefit more from radioembolization than sorafenib. Recently, a large study showed significantly better response rates and less adverse events after radioembolization than after sorafenib, even after correction of confounders (Table 5). Survival was similar. Patients are currently being
recruited in the YES-P, SARAH and SIRVENIB trials in which sorafenib and radioembolization will be compared in a randomized controlled setting. Combining both treatments seems beneficial with manageable toxicities, based on the results of a phase II study in the Asia-Pacific Trial. (63) This is currently under investigation in the SORAMIC-trial (resin microspheres) and the STOP-HCC trial (glass microspheres). Patients, who are ineligible or poor candidates for TACE are randomized in two groups: sorafenib combined with radioembolization compared to sorafenib alone. Even though radioembolization is currently not incorporated in the BCLC scheme and the results of the above-mentioned trials are pending, for selected patients radioembolization can be positioned between TACE and sorafenib (Figure 4).

In patients with focal or limited disease, ineligible for surgical resection or RFA, radioembolization may provide an interesting alternative using glass microspheres: Radiation segmentectomy is meant to provide an ablating radiation dose (>200 Gy) by (super)selective catheterization. By selective targeting, necrosis is induced in a limited portion of the liver including the tumor, thus sparing radiation dose to healthy liver parenchyma. Vouche et al. described a high ORR (88%) and median OS (53.4 months) using this technique in solitary HCC < 5 cm. (64) In their cohort, 33% was amiable for liver transplantation after radiation segmentectomy. At pathological examination of the native liver specimens, 100% necrosis and > 90% necrosis was found in respectively 52% and 48%. (64) In HCC, the downstaging success rate with radioembolization is around 50% (range 29% – 67%) with an median time to downstaging of 3.1 – 4 months. (65) In downstaging HCC, radioembolization is a suitable alternative for TACE, but downstaging should not be restricted to HCC alone. (65)

The current ESMO guideline on mCRC states that in patients with liver-limited disease and unresectable liver metastases failing available chemotherapeutic regimens, radioembolization using resin microspheres prolongs time to tumor progression. (66) Results in heavily pre-treated patients with chemoresistant mCRC have been consistent over the years,
making salvage treatment with radioembolization a widely accepted indication. According to a recent systematic review, treated patients have failed a median of three chemotherapeutic regimens prior to radioembolization.(67) Left untreated, patients with chemorefractory liver metastases have a median survival (MS) of only 5 - 7 months.(68-70) Nonetheless, in this population with an overall poor prognosis, following radioembolization a mean ORR of 31%, median PFS of 9 months and median OS of 12 months are obtained (Table 5).(67) Several randomized controlled trials are ongoing to establish the role of radioembolization for mCRC.(Figure 5) The addition of radioembolization to first-line chemotherapy regimens are currently being investigated in the SIRFLOX, FOXFIRE and SIR-step trial (all using resin microspheres). After first-line failure, the EPOCH trial will randomize patients in second-line chemotherapy with or without radioembolization (glass microspheres).

Another relatively new application of radioembolization prior to surgical resection, is the induction of hypertrophy of the contralateral lobe by radioembolization of the diseased lobe. After portal vein embolization (PVE), 17.5% of patients are ineligible for surgical resection due to tumor progression and 4.8% fails sufficient hypertrophy of the functional liver remnant.(71) Compared to PVE, the induction of hypertrophy by radioembolization is similar, however, it takes a longer period of time. A degree of hypertrophy of approximately 35% (8.9% - 57%) can be obtained in 3-4 months.(65) Theoretically, the main benefit of radioembolization is simultaneous tumor treatment, reducing the number of drop-outs due to disease progression.

Unresectable intrahepatic cholangiocarcinoma (ICC), left untreated, has a OS of less than 8 months and with gemcitabine and cisplatin OS is 11.7 months.(72, 73) After radioembolization OS of 15.5 months can be reached.(72) Repeated radioembolization can lead to local disease control for a longer period of time (Supplemental Figure 1). Radioembolization prior to surgical resection, like in HCC and mCRC, could be promising in ICC as well. Downstaging occurs in 10% and inducing contralateral hypertrophy seems feasible.(65, 72) In a
small cohort combining radioembolization with chemotherapy, downstaging occurred in 22%, significant hypertrophy of contralateral lobes was seen in all patients, and 18% was radically resected.(74) In general, these results for ICC are promising, but current literature is limited.

The heterogeneous group of neuro-endocrine tumors (NET) has a lower incidence than aforementioned tumors, though hepatic involvement in NET is common and is the greatest incriminating factor on survival (disease free survival 20 months with >4 hepatic metastases versus 46 months with ≤4 hepatic metastases).(75) The majority of patients presents with multifocal hepatic disease and is ineligible for resection or RFA.(76) Conventional treatments (i.e. somatostatin analogs) and newer biologicals (i.e. sunitinib and everolimus) improve survival, however ORR are poor. Due to the hypervascular nature of the hepatic metastases, NET are prime candidates for radioembolization. In a meta-analysis including 414 patients, the pooled ORR was 50%, disease control rate was 86% and OS was 28.5 months.(77)(Table 5) Data reporting response rates based on the primary tumor origin and according to the WHO histologic grading system are needed.

CONCLUSION

Hepatic yttrium-90 radioembolization continues to develop at a rapid pace. Clinical research is expanding indications in many different tumor types, overcoming technical angiographic challenges, fine-tuning the application of dosimetry and optimizing quantitative imaging in daily practice.

DISCLOSURES AND ACKNOWLEDGEMENTS

No financial disclosures or acknowledgements to report.
REFERENCES


FIGURE 1. Coronal reconstructions of a C-arm CT in a patient prior to radioembolization. During angiography the catheter was positioned in the proximal left hepatic artery. A. The C-arm CT illustrates arterial flow of contrast towards the pancreatic head / duodenal region, supplied by a supraduodenal artery (arrowheads), missed during digital subtraction angiography. Based on this additional finding, the artery was occluded. B. After coil embolization, contrast flow towards the gastrointestinal tract was resolved.
FIGURE 2. Illustrating a patient with an HCC recurrence in segment 7, who had previously undergone primary segmental resection with curative intent, cholecystectomy and biliary stent placement. The gastroduodenal artery was coil embolized (stars). Injection positions in the left hepatic artery for $^{99m}$Tc-MAA (A) and $^{90}$Y-resin microspheres (B) (subsequent injection position in right hepatic artery not shown). Discrepancy of distribution between $^{99m}$Tc-MAA-SPECT/CT (C) and $^{90}$Y-PET/CT (D) can be acknowledged, in which the distribution in segment 4 is underestimated by $^{99m}$Tc-MAA. These differences occurred even though the exact same 2D injection position was used in both angiographic procedures (arrows). This may be caused by the randomly shaped $^{99m}$Tc-MAA versus spherical microspheres, bolus injection $^{99m}$Tc-MAA versus intermittent injection $^{90}$Y-microspheres, in plane (3D) catheter tip position differences, and
a different number of particles injected during the scout dose, inducing differences in flow dynamics.

FIGURE 3. Illustrating a patient with a large HCC of 12 cm in the right lobe on a T1-weighted MRI sequences in coronal plane. A. Prior to radioembolization, B. illustrating tumor shrinkage after radioembolization. C. T1 gadolinium enhanced MRI with fat suppression in an axial plane during the arterial phase (20 sec post-injection), illustrating the hypervascular tumor. D. On the same sequence after radioembolization, a large area of necrosis in the tumor can be acknowledged.
FIGURE 4. BCLC staging system with a proposal for radioembolization in the treatment paradigm. Due to the overlapping applicability of radioembolization in intermediate and advanced stage HCC, these stages have been combined in this proposal. *Size of tumors has been included in this BCLC scheme, however the exact size limits need to be investigated further.
FIGURE 5. Schematic view on the evolving application of radioembolization in metastatic colorectal cancer (mCRC) and current trials. At present, radioembolization is mainly applied in a salvage setting, however, many clinical trials focus on bringing radioembolization to the forefront of the mCRC treatment algorithm in a first or second line setting.
### TABLE 1. Common indications, relative and absolute contra-indications for radioembolization

<table>
<thead>
<tr>
<th>Indications</th>
<th>Relative contra-indications</th>
<th>Absolute contra-indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not amenable for surgical resection, liver transplantation or curative ablative therapies</td>
<td>Portal vein thrombosis of the main branch</td>
<td>Extensive and untreated portal hypertension</td>
</tr>
<tr>
<td>Not amenable for, refractory to, or not willing to receive chemotherapeutic alternatives</td>
<td>Abnormalities of the bile ducts or stents. Exceptions: papillotomy and cholecystectomy</td>
<td>Life expectancy &lt; 3 months</td>
</tr>
<tr>
<td>Compensated or early decompensated (Child-Pugh ≤ B7) liver cirrhosis</td>
<td>Serum bilirubin &gt; 34.2 µmol/L (2 mg/dL)</td>
<td>Active hepatitis</td>
</tr>
<tr>
<td>Performance state (ECOG) ≤ 2</td>
<td>Leukocytes &lt; 2 x10⁹/L and/or platelet count &lt; 60 x10⁹/L</td>
<td>Extrahepatic deposition of ⁹⁹mTc-MAA on SPECT/CT or contrast on C-arm CT</td>
</tr>
<tr>
<td>Liver-only or liver-dominant disease</td>
<td>Glomerular filtration rate &lt; 35 mL/min</td>
<td>Unacceptable lung shunt*</td>
</tr>
<tr>
<td>Pre-operative indications</td>
<td>INR &gt; 1.5</td>
<td></td>
</tr>
</tbody>
</table>

*Lung absorbed dose < 30 Gy in a single session and < 50 Gy in multiple sessions.*
TABLE 2. Current literature on liver abscesses and bilidigestive anastomoses after radioembolization

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Total</th>
<th>BDA</th>
<th>Incidence liver abscess</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atassi 2008(13)</td>
<td>Radioembolization</td>
<td>327</td>
<td>NR</td>
<td>0.3% of total</td>
<td>0.3% = 1 patient with a bilidigestive anastomosis</td>
</tr>
<tr>
<td>Cholapranee 2014(17)</td>
<td>Radioembolization + prophylaxes*</td>
<td>16</td>
<td>11</td>
<td>0%</td>
<td>5/16 had biliary stents</td>
</tr>
<tr>
<td></td>
<td>Chemoembolization + prophylaxes*</td>
<td>13</td>
<td>5</td>
<td>23% of total</td>
<td>Not reported how many patients with a liver abscess had a bilidigestive anastomosis</td>
</tr>
<tr>
<td>Geisel 2014(16)</td>
<td>Radioembolization</td>
<td>168</td>
<td>9</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Korkmaz 2014(78)</td>
<td>Radioembolization†</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mascarenhas 2011(18)</td>
<td>Radioembolization†</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Levofloxacin 500 mg daily and metronidazole 500 mg twice daily for 2 weeks. Additionally 1000 mg neomycin and 1000 mg erythromycin thrice on the day of the intervention. †Case report.

Legend: BDA = numbers of patient with a bilidigestive anastomoses, NR = Not reported.
### TABLE 3. Three most common culprit vessels (20, 21, 23, 79, 80)

<table>
<thead>
<tr>
<th>Origins</th>
<th>Gastroduodenal artery</th>
<th>Cystic artery</th>
<th>Right gastric artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common hepatic artery</td>
<td>Right hepatic artery</td>
<td>Left hepatic artery (42%)</td>
</tr>
<tr>
<td></td>
<td>Other (3%)</td>
<td>Other (2%)</td>
<td>Proper hepatic artery (40%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastroduodenal (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right hepatic artery (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Common hepatic artery (3%)</td>
</tr>
<tr>
<td>Possible complication</td>
<td>Gastroduodenal ulcer</td>
<td>Radiation induced cholecystitis</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td>(0-7%)</td>
<td></td>
</tr>
<tr>
<td>Coil embolization?</td>
<td>Not needed when:</td>
<td>Not needed. Microcatheter</td>
<td>Not needed when:</td>
</tr>
<tr>
<td></td>
<td>1) Hepatopetal flow</td>
<td>distal of origin is preferred.</td>
<td>1) Distal placement of microcatheter (&gt; 4-5 cm)</td>
</tr>
<tr>
<td></td>
<td>2) Distal placement of microcatheter (&gt; 4-5 cm)</td>
<td></td>
<td>2) No extrahepatic contrast on C-arm CT</td>
</tr>
<tr>
<td></td>
<td>3) No extrahepatic contrast on C-arm CT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 4. Pre-treatment activity calculation methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Activity calculation equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical(33)</td>
<td>Tumor load ≤ 25% = 2.0 GBq whole-liver delivery, Tumor load 25-50% = 2.5 GBq whole liver delivery, Tumor load ≥ 50% = 3.0 GBq whole liver delivery</td>
</tr>
<tr>
<td>Body surface area(33)</td>
<td>$A(\text{GBq}) = (\text{BSA} - 0.2) + \left(\frac{\text{tumor volume}}{\text{tumor volume} + \text{liver volume}}\right)$ in which: $\text{BSA} = 0.20147 \times \text{height(m)}^{0.725} \times \text{weight(kg)}^{0.429}$</td>
</tr>
<tr>
<td>Partition(33)</td>
<td>$A(\text{GBq}) = \frac{D(\text{Gy}) \times \left(\frac{T}{N} \times \frac{\text{Mass}<em>{\text{tumor}}(\text{kg})}{\text{Mass}</em>{\text{liver}}(\text{kg})}\right)}{49670 \times (1 - \text{Lung shunt fraction})}$ in which, based on MAA-SPECT/CT: $\frac{T}{N} = \frac{\text{Activity}<em>{\text{tumor}}(\text{GBq})}{\text{Activity}</em>{\text{liver}}(\text{GBq})}$</td>
</tr>
<tr>
<td>Glass microspheres(34)</td>
<td>$A(\text{GBq}) = \frac{D(\text{Gy}) \times \text{Mass}_{\text{liver}}(\text{kg})}{50 \times (1 - \text{Lung shunt fraction})}$ with an upper limit of lung shunt activity: $\text{Lung shunt fraction(%)} \times A(\text{GBq}) = 0.61 \text{ GBq}$</td>
</tr>
</tbody>
</table>
### TABLE 5. Landmark studies on response and survival in liver malignancies

<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
<th>Tumor</th>
<th>Treatment</th>
<th>N</th>
<th>Respon se criteria</th>
<th>CR %</th>
<th>PR %</th>
<th>SD %</th>
<th>PD %</th>
<th>TTH months</th>
<th>MS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolligs 2014(60)</td>
<td>Pilot randomized controlled trial</td>
<td>HCC BCLC A-C Child Pugh ≤ B7</td>
<td>Radioembolization</td>
<td>13</td>
<td>RECIST 1.0</td>
<td>0</td>
<td>30.8</td>
<td>46.2</td>
<td>15.4</td>
<td>3.7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemoembolization</td>
<td>15</td>
<td></td>
<td>0</td>
<td>13.3</td>
<td>60.0</td>
<td>20.0</td>
<td>3.6</td>
<td>NA</td>
</tr>
<tr>
<td>Gramenzi 2014‡(62)</td>
<td>Single center, prospective cohort</td>
<td>HCC BCLC B-C Child Pugh ≤ B7</td>
<td>Radioembolization</td>
<td>63</td>
<td>mRECIST</td>
<td>14.3</td>
<td>53.9</td>
<td>14.3</td>
<td>17.5</td>
<td>3</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62.5</td>
<td>18.8</td>
<td>18.7</td>
<td>3</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sorafenib</td>
<td>73</td>
<td></td>
<td>0</td>
<td>9.5</td>
<td>41.9</td>
<td>48.6</td>
<td>5</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.4</td>
<td>37.5</td>
<td>53.1</td>
<td>3</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Al-Adra 2014(72)</td>
<td>Systematic review</td>
<td>Intrahepatic cholangiocarcinoma</td>
<td>Radioembolization</td>
<td>29</td>
<td>Pooled analysis</td>
<td>0</td>
<td>28</td>
<td>54</td>
<td>18</td>
<td>NA</td>
<td>15.5</td>
</tr>
<tr>
<td>Devcic 2014(77)</td>
<td>Meta-analysis</td>
<td>Neuroendocrine tumor</td>
<td>Radioembolization</td>
<td>43</td>
<td>Pooled analysis</td>
<td>50</td>
<td>36</td>
<td>14</td>
<td>NA</td>
<td>28.5</td>
<td></td>
</tr>
<tr>
<td>Saxena 2014(67)</td>
<td>Systematic review</td>
<td>Metastatic colorectal cancer</td>
<td>Radioembolization</td>
<td>97</td>
<td>Pooled analysis</td>
<td>0</td>
<td>31</td>
<td>40.5</td>
<td>17.5</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

*Percentages, †Months, ‡Italicized numbers are the confounder corrected results,

Legend: CR = complete response, MS = median survival, N = number of patients, NA = not available, PD = progressive disease, PR = partial response, SD = stable disease, TTHP = median time to hepatic progression.
Yttrium-90 hepatic radioembolization: an update on current practice and recent developments


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